



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Wang, et al.

Group No.: 1646

Serial Number: 09/605,577

Examiner: J Seharaseyon

Filed: 6/28/00

Title: STABILIZED INTERLEUKIN-2

#14
M.Q.J
10/16/02

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION under 37 C.F.R. 1.132 of Wei Wang

I, Wei Wang, hereby declare that:

I am a Staff Scientist at Bayer Corporation at Berkeley, and have been since 1995.

I received an undergraduate degree in Pharmacy from Shandong University in China in 1982, and a Doctor of Philosophy degree in Pharmaceutical Sciences from University of Southern California in 1992. From 1992 to 1995, I worked at InsiteVision as a formulation development scientist.

During my career, I have concentrated in certain pharmaceutical areas, including formulation development of proteins, peptides, and other small drug molecules, membrane transport of drugs, and development of analytical methodologies.

I am the author or co-author of more than 20 journal publications or scientific meeting presentations. Recently, I wrote two comprehensive review articles regarding protein stability and formulation. They are "Lyophilization and Development of Solid Protein Pharmaceuticals" published in Int. J. Pharm. (V203, P1-6) in 2000, and "Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals" published in Int. J.

Pharm. (V185, P129-188) in 1999. I consider myself a true expert in the area of protein formulation and stabilization.

I have read the Office Action dated 07/30/2002, Paper No. 12; and the references referred to in the Office Action. The Office Action makes a number of assumptions regarding the stabilization of aqueous materials and the stabilization of lyophilized material, which I wish to address.

On Page 3, the Office Action alleges that the Patel patent discloses a stabilized formulation that anticipates my work. In point of fact the Office Action has disregarded a clearly stated limitation in the Patel patent. Namely, Patel says in his claims and in his specification that his formula is directed to aqueous stability.

The stabilization of aqueous formulations and lyophilized formulations are very different. A skilled practitioner working with protein stabilization strategies would not conclude that the technology, materials or methods that are successful in stabilizing an aqueous formulation would be the same or similar to the technology, materials or methods necessary to the stabilization of lyophilized proteins.

Pharmaceutical chemists select protein stabilization agents based upon certain accepted theories of stabilization. The leading theory of effective *lyophilized stabilization* is called the *water replacement hypothesis*, while *liquid state stabilization* appears to conform to a theory known as *preferential exclusion*.

In *the water replacement hypothesis* (lyophilized stabilization) stabilizing agents are selected on the basis of their ability to replace the water molecules that surround each protein molecule. The goal of this approach is to replace each protein's hydration shell with agents that form hydrogen bonds with the protein and substantially reduce the chance of protein to protein interactions (which often leads to aggregation) while at the same time maintaining the maximum of each molecule's original 3-D structure. In *the preferential exclusion theory* (liquid stabilization) stabilizing agents are added to the aqueous media but are preferentially excluded from the surface of the protein to achieve protein stabilization. The mechanisms that drive each of these two theories are different and the stabilizing agents selected must fulfill different functions.

Since protein stabilization mechanisms are different in liquid and solid states, many effective protein stabilizers in solution do not stabilize proteins during lyophilization storage. As examples: It is well known that CaCl₂ stabilizes elastase (20 mg/ml) in 10 mM sodium acetate (liquid stabilization) but causes the lyophilized protein cake to collapse and lose activity. In liquid stabilization KCl (at 500 mM) effectively protects lactate dehydrogenase from thermal inactivation at 50 C but does not protect the protein activity at all during lyophilization.

For the reasons I have stated above, I want to make clear that a skilled practitioner would not conclude that the agents used to stabilize aqueous protein solutions would also stabilize the same protein in a lyophilized condition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed: Wei Wang
Wei Wang, Ph.D.

Date: 9/27/2002